News and Resources from the National Institutes of Health

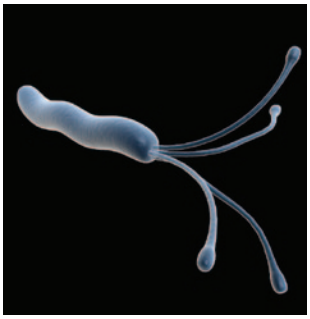
Digestive Diseases NEWS

National Digestive Diseases Information Clearinghouse

Winter 2011

NIDDK-supported Research Offers New Knowledge for Studying Effects of *H. pylori* Infection

Scientists studying *Helicobacter pylori (H. pylori)* may have uncovered new knowledge thanks to research funded by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). Their research sheds light on the understanding of bacterial genes involved in repression of the gastric proton pump and of acid secretion.



H. pylori infection of the gastric mucosa causes gastritis, inhibits acid secretion, and may lead to the development of cancer. Acid secretion is mediated by the H,K-ATPase enzymatic proton pump in parietal cells that contains a catalytic α subunit (HKα). The same scientists had previously shown that *H. pylori* induces nuclear factor-kB (NF-kB) binding to and repression of HKα promoter activity in gastric epithelial cells. *H. pylori* eradication in humans increases HKα synthesis and restores acid secretion.

H. pylori strains containing a *cag* pathogenicity island (PAI) genetic locus cause severe gastric inflammation, ulceration, and increased risk of gastric cancer. Several *cag* PAI genes encode proteins that assemble into a type IV secretion system (T4SS) spanning the inner and outer bacterial membranes, which allows *H. pylori* adherence to host cells and enables transfer of virulence factors.

"This study identified the *cag* PAI as instrumental in *H. pylori*-induced HKα repression," stated Adam Smolka, Ph.D., Medical University of South Carolina, and colleagues. "The study introduces a novel and potentially informative model for studying the molecular pathophysiology of human *H. pylori* infection, allowing for the first time controlled exposure of human gastric mucosa to different *H. pylori* strains and refined pharmacological interventions to dissect the affected cellular signaling pathways."

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NIDDK
NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES

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Adam Smolka, Ph.D.
Medical University of South Carolina, and colleagues

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The study showed that a small subset of *H. pylori cag* PAI genes play a role in repression of HKα transcription leading to inhibition of acid secretion. Researchers infected gastric epithelial cells and gastric biopsies with *cagL, cagM,* and *cagE* deficient strains of *H. pylori* and found that these strains failed to repress HKα promoter activity.

These results implicated gene products of *H. pylori cag* PAI genes *cagL, cagM,* and *cagE* in repression of HKα synthesis following acute infection and showed that repression is reflected in acid secretory inhibition. Researchers also showed that the *H. pylori* virulence factor CagA, which is injected into gastric cells upon infection, is involved in HKα repression.

As researchers understand how various *H. pylori* genes affect acid secretion, doctors may one day use this knowledge of the *H. pylori* genotype for therapeutic decision-making by identifying high-risk patients who warrant eradication therapy.

The National Digestive Diseases Information Clearinghouse, an information dissemination service of the NIDDK, has fact sheets and easy-to-read booklets about digestive disorders and *H. pylori*. For more information and to obtain copies, visit *www.digestive.niddk.nih.gov.* ■

Would you like to know more about NIDDK-supported research?

The National Institutes of Health (NIH) provides access to a variety of reporting tools, reports, data, and analyses of NIH research activities at the Research Portfolio Online Reporting Tools (RePORT) website, *www.projectreporter.nih.gov/reporter.cfm.* One of the tools available is RePORT Expenditures and Results (RePORTER), which allows users to search a repository of NIH-funded research projects and access and download publications and patents resulting from NIH funding. ■

Digestive Diseases
NEWS

Digestive Diseases News, an email newsletter, is sent to subscribers by the National Digestive Diseases Information Clearinghouse (NDDIC). The newsletter features news about digestive diseases, special events, patient and professional meetings, and new publications available from the NDDIC and other organizations.

You can read or download a PDF version or subscribe to the newsletter at *www.digestive.niddk.nih.gov/about/newsletter.htm.*

Executive Editor: Stephen P. James, M.D.

Dr. James is the director of the Division of Digestive Diseases and Nutrition within the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). As director, Dr. James oversees planning, implementation, and evaluation of a national research effort focused on gastrointestinal, pancreatic, hepatobiliary, and nutrition diseases and conditions. Before joining the NIDDK in 2001, Dr. James directed the division of gastroenterology at the University of Maryland's School of Medicine for 10 years.

Crohn's Disease Is Associated with Restless Legs Syndrome

Researchers investigating a link between restless legs syndrome (RLS) and Crohn's disease (CD) uncovered results that demonstrate RLS occurs frequently in people with CD and appears to be a possible extraintestinal manifestation of CD. This research appeared in the February 2010 issue of *Inflammatory Bowel Disease.*

"Overall, RLS was found to be a common comorbid condition in patients with CD. The incidence of RLS in patients with CD reported in this study was greater than the incidence of many of the known extraintestinal manifestations of CD."

Leonard B. Weinstock, M.D.
Department of Internal Medicine, Washington University School of Medicine, St. Louis, MO, and colleagues

CD is an ongoing disorder that causes inflammation of the digestive tract, also referred to as the gastrointestinal (GI) tract. CD can affect any area of the GI tract, from the mouth to the anus, but it most commonly affects the lower part of the small intestine, called the ileum.

CD has a variety of possible extraintestinal manifestations: arthritis, skin problems, kidney stones, gallstones, and liver diseases. This study is the first to show central nervous system (CNS) manifestations of CD.

RLS is a condition in which a person experiences extreme leg discomfort while sitting or lying down. RLS may be primary or secondary to a number of disorders. Secondary RLS occurs in a variety of patient populations, including pregnant women and people with end-stage renal disease, iron-deficiency anemia, rheumatoid arthritis, diabetes, Parkinson's disease, or fibromyalgia.

Because both CD and RLS are associated with iron deficiency, GI tract inflammation, and bacterial overgrowth, researchers designed the study to investigate the potential link between these two disorders.

"Overall, RLS was found to be a common comorbid condition in patients with CD," stated Leonard B. Weinstock, M.D., Department of Internal Medicine, Washington University School of Medicine, St. Louis, MO, and colleagues. "The incidence of RLS in patients with CD reported in this study was greater than the incidence of many of the known extraintestinal manifestations of CD."

A total of 272 patients with CD participated in the study, and researchers found a 43 percent incidence rate and 30 percent prevalence rate of RLS in patients with CD, compared with a 9 percent prevalence rate in the control group. RLS symptoms occurred during or after the onset of CD symptoms in the majority of patients, suggesting a link between CD and RLS.

Systemic disease symptoms of CD include malnutrition and anemia. Iron deficiency is the main cause of anemia in CD as a consequence of dietary restrictions, malabsorption, and intestinal bleeding. People at risk for iron deficiency are also at risk for RLS. The study showed that current systemic iron deficiency was not associated with RLS in patients with CD, but significantly more patients with CD and RLS reported a history of iron deficiency than those without RLS symptoms.

Previous studies have demonstrated an association of small intestinal bacterial overgrowth with CD in the ileum. The results of this study suggest ileum involvement in patients with CD may be a risk factor for RLS. The researchers hypothesized that inflammation attributable to other systemic and GI-related disorders, such as CD, results in an iron deficiency in the CNS, causing RLS.

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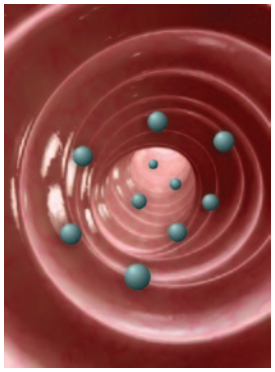
Drug-loaded Nanoparticles May Offer Precise Targeting in Treatment of Inflammatory Bowel Disease



"KPV-loaded NPs efficiently reduced the severity of intestinal colitis. Given that KPV affects inflammatory responses in both epithelial and immune cells, it is reasonable to suggest that, under the delivery conditions used in the present study, low doses of KPV would affect the inflammatory responses of these two cell types."

Hamed Laroui, Ph.D.
Division of Digestive Diseases, Department of Medicine, Emory University

Research funded by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) could one day allow doctors to deliver drug-loaded nanoparticles (NPs) in the treatment of inflammatory bowel disease (IBD). Researchers from the Department of Medicine at Emory University engineered NPs to deliver anti-inflammatory agents to the colon and assessed its therapeutic efficacy in a mouse model of colitis.

One of the challenges in treating IBD is targeting the site of inflammation. Another problem is that most existing treatments are associated with significant side effects. "A major advance in therapeutic strategies in diseases such as IBD would be the ability to target drugs to the site of the inflammation in sufficient quantities to maximize local drug concentration and minimize systemic side effects," stated Hamed Laroui, Ph.D., Division of Digestive Diseases, Department of Medicine, Emory University.

In the past, doctors have had difficulty targeting drugs to the site of inflammation because of the lack of vehicles that could carry sufficient drugs or that could be released at the site of inflammation. In addition, delivering drugs to the colon runs the risk of enzyme degradation and systemic absorption. The researchers decided to use NPs to deliver the anti-inflammatory tripeptide Lys-Pro-Val (KPV).

This study showed KPV-loaded NPs were able to rapidly release KPV, which reduced intestinal inflammation. Because KPV is delivered by NPs in close proximity to the cell membrane, researchers found they could use a low KPV dose. Researchers also showed that KPV-loaded NPs are well protected during transit through the gastric gland and small intestine.

The researchers compared the dose of KPV-loaded NPs with KPV in free solution and found that the effective dose of KPV was 12,000 times lower when administrated via encapsulated KPV-loaded NPs compared with KPV in free solution.

The low dose of KPV raised concern among the researchers whether the concentration was sufficient to reduce intestinal inflammation. They concluded that "KPV-loaded NPs efficiently reduced the severity of intestinal colitis. Given that KPV affects inflammatory responses in both epithelial and immune cells, it is reasonable to suggest that, under the delivery conditions used in the present study, low doses of KPV would affect the inflammatory responses of these two cell types."

The researchers concluded that encapsulated drug-loaded NPs are a versatile drug-delivery system, with the ability to overcome physiological barriers and target low concentrations of the anti-inflammatory drug KPV to inflamed areas to relieve symptoms of IBD.

The National Digestive Diseases Information Clearinghouse, an information dissemination service of the NIDDK, has fact sheets and easy-to-read booklets about digestive disorders, including IBD. For more information and to obtain copies, visit *www.digestive.niddk.nih.gov.* ■

HHS Launches Healthy People 2020

The U.S. Department of Health and Human Services (HHS) officially launched Healthy People 2020 on December 2, 2010, at the George Washington University in Washington, D.C. The event marked the formal release of the decade's national health promotion and disease prevention objectives.

"[Healthy People 2020] should no longer be known primarily as a print-based reference book to be kept on the shelf for a decade. It should also be a Web-accessible database that is searchable, multilevel, and interactive."

Advisory Committee on National Health Promotion and Disease Prevention Objectives for 2020

Each decade since 1980, the HHS has released a comprehensive set of national public health objectives. Known as Healthy People, the initiative has been grounded in the notion that setting objectives and providing benchmarks to track and monitor progress can motivate, guide, and focus action.

The HHS convened the Secretary's Advisory Committee on National Health Promotion and Disease Prevention Objectives for 2020 to aid in the process of developing the next decade's guidelines. The Advisory Committee was charged with providing advice and consultation to the Secretary: 1) to facilitate the development and implementation of national health promotion and disease prevention goals and objectives, and 2) to inform the development of initiatives that will occur during initial implementation of the goals and objectives.

Healthy People 2020 should assist federal agencies in setting priorities and in providing funding and support to organizations and institutions that are able to help achieve the objectives. The Advisory Committee stated that Healthy People 2020 "should no longer be known primarily as a print-based reference book to be kept on the shelf for a decade. It should also be a Web-accessible database that is searchable, multilevel, and interactive."

Healthy People 2020's overarching goals include eliminating preventable disease, disability, injury, and premature death; achieving health equity, eliminating disparities, and improving the health of all groups; creating social and physical environments that promote good health for all; and promoting healthy development and behaviors across every stage of life.

Members of the public health community—especially federal, state, and local health agencies—have traditionally been viewed as the primary audiences for Healthy People. The Advisory Committee proposes that Healthy People 2020 be designed for use by a wider range of groups in both the public and private sectors. Tailored messages and products are needed to make Healthy People useful for this expanded audience-base, which should include the general public, voluntary organizations, faith-based organizations, businesses, health care providers, decision-makers, researchers, community-based organizations, grass-roots advocates, and others whose actions have significant health consequences.

The December 2 launch program included remarks by HHS Assistant Secretary for Health Howard K. Koh, M.D., and members of the Advisory Committee; an introduction and orientation to the Healthy People 2020 website and objectives; and a panel discussion about the uses of Healthy People 2020.

For more information about the Healthy People 2020 initiative, please visit *www.healthypeople.gov/HP2020.* ■

Administration Announces Regulations Requiring New Health Insurance Plans to Provide Free Preventive Care

The U.S. Departments of Health and Human Services (HHS), Labor, and the Treasury issued new regulations in July requiring new private health plans to cover evidence-based preventive services and eliminate cost-sharing requirements for such services. The new rules will help Americans gain easier access to services such as blood pressure, diabetes, and cholesterol tests; many cancer screenings; routine vaccinations; prenatal care; and regular wellness visits for infants and children.

"Getting access to early care and screenings will go a long way in preventing chronic illnesses like diabetes, heart disease, and high blood pressure."

Michelle Obama
First Lady

"Today, too many Americans do not get the high-quality preventive care they need to stay healthy, avoid or delay the onset of disease, lead productive lives, and reduce health care costs," said HHS Secretary Kathleen Sebelius. "From the Recovery Act to the First Lady's Let's Move Campaign to the Affordable Care Act, the Administration is laying the foundation to help transform the health care system from a system that focuses on treating the sick to a system that focuses on keeping every American healthy."

Chronic diseases, such as heart disease, cancer, and diabetes, are responsible for seven of 10 deaths among Americans each year and account for 75 percent of the nation's health spending—and often are preventable. Nationally, Americans use preventive services at about half the recommended rate. An estimated 11 million children and 59 million adults have private insurance that does not adequately cover immunization, for instance. Studies have shown that cost sharing, including deductibles, coinsurance, and copayments, reduces the likelihood that people will use preventive services.

"Getting access to early care and screenings will go a long way in preventing chronic illnesses like diabetes, heart disease, and high blood pressure," said First Lady Michelle Obama. "And good [preventive] care will also help tackle an issue that is particularly important to me as First Lady and as a mother—and that is the epidemic of childhood obesity in America today. These are important tools, and now it's up to us to use them."

"One of the best ways to improve the quality of your life—and control health care costs—is to prevent illness in the first place," said Second Lady Jill Biden. "Focusing on prevention and early treatment makes more sense than trying to play catch-up with a potentially deadly disease. Quite simply, these [preventive] services will save lives."

Under the recently issued regulations, new health plans beginning on or after September 23, 2010, must cover preventive services that have strong scientific evidence of their health benefits, and these plans may no longer charge a patient a

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NIH Pays Tribute to the First Woman Appointed Director of an NIH Institute, Ruth L. Kirschstein

Current and former National Institutes of Health (NIH) scientists and staff, as well as members of Congress, honored Ruth L. Kirschstein, M.D., the first woman appointed director of an NIH Institute, for the positive impact she made as a leader in the scientific community.

"Ruth Kirschstein was a legendary scientist and administrator."

David Obey
U.S. Representative, Chairman of the House Appropriations Committee

"Ruth embodied the spirit of NIH. She was an icon. She was loved and admired by so many at the NIH, across the medical research community, among hundreds of members of Congress, and around the world. There are few at the NIH who have not been touched by her warmth, wisdom, interest, and mentorship," said Francis S. Collins, M.D., Ph.D., director of the NIH.

Kirschstein, who passed away in 2009, was honored in 2010 with a tribute and symposium in her honor that featured four sessions with 11 featured speakers and ended with a reception. Scientists and researchers who received funds from the Ruth L. Kirschstein National Research Service Award presented the sessions. The awards have supported the work of thousands of researchers, and the quality of their research has elevated the program to the ranks of Fulbright Awards and Rhodes Scholarships.

As the first woman director of an NIH Institute—the National Institute of General Medical Sciences (NIGMS)—Kirschstein was known for mentoring young researchers, especially women and minorities. In 1993, Kirschstein became acting director of the NIH, and then served as the deputy director under NIH Director Harold Varmus for the next 6 years. She was acting director again from 2000 to 2002.

A Brooklyn native, Kirschstein wanted to be a doctor from a young age and fulfilled her dream after graduating *magna cum laude* in 1947 from Long Island University. She then went to Tulane University School of Medicine, where she was one of 10 women in a class of 100 men.

She interned in medicine and surgery at Kings County Hospital in Brooklyn and completed residencies in pathology in Detroit, New Orleans, and the then new NIH Clinical Center. In 1957, Kirschstein joined the Federal Government, beginning a 15-year stint as an experimental pathologist at the NIH Division of Biologics Standards, now known as the U.S. Food and Drug Administration (FDA) Center for Biologics Evaluation and Research.

In her first major accomplishment as a scientist, Kirschstein led the development of a safety test for the polio vaccine in the 1950s and 1960s. Ultimately, her work led to widespread adoption of the Sabin oral vaccine, especially in developing countries. Kirschstein continued to develop tests for the safety of vaccines for other diseases, including measles.

In 1974, after 2 years with the FDA, Kirschstein was appointed director of the NIGMS, a post she held for nearly 20 years. One of her most significant accomplishments as NIGMS director was her dedication to funding HIV/AIDS research and helping to establish the Genbank nucleic acid sequence database, which has been a

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copayment, coinsurance, or deductible for these services when they are delivered by a network provider. Specifically, these recommendations include the following:

- **Evidence-based preventive services.** The U.S. Preventive Services Task Force, an independent panel of scientific experts, rates preventive services based on the strength of the scientific evidence documenting their benefits. Preventive services with a "grade" of A or B—such as tobacco cessation counseling and screenings for breast and colon cancer, vitamin deficiencies during pregnancy, diabetes, high cholesterol, and high blood pressure—will be covered under these rules.
- **Routine vaccines.** Health plans will cover a set of standard vaccines recommended by the Advisory Committee on Immunization Practices. Such vaccines range from routine childhood immunizations to periodic tetanus shots for adults.
- **Preventive care for children.** Health plans will cover preventive care for children recommended under the *Bright Futures* guidelines, developed by the Health Resources and Services Administration with the American Academy of Pediatrics. These guidelines provide pediatricians and other health care professionals with recommendations on the services they should provide to children from birth to age 21 to keep them healthy and improve their chances of becoming healthy adults. The types of services that will be covered include regular pediatrician visits, vision and hearing screenings, developmental assessments, immunizations, and screening and counseling to address obesity and help children maintain a healthy weight.
- **Preventive care for women.** Health plans will cover preventive care provided to women under both the Task Force recommendations and new guidelines being developed by an independent group of experts, including doctors, nurses, and scientists, which are expected to be issued by August 1, 2011.

More information about the Affordable Care Act's new rules on preventive care can be found at *www.healthcare.gov/law/about/provisions/services/index.html.*

The regulations can be found at *www.healthcare.gov/center/regulations/prevention/regs.html.* ■

Ruth L. Kirschstein, continued from page 7

critical tool for biomedical research. She championed myriad programs in basic biomedical research and research training that have helped to transform biomedical research.

"Ruth Kirschstein was a legendary scientist and administrator . . . a pioneer . . . a champion for the advancement of women and minorities in biomedical research . . . a strong advocate for research training, especially interdisciplinary predoctoral programs," said U.S. Representative David Obey, chairman of the House Appropriations Committee.

Kirschstein remained active at the NIH in her later years as a senior adviser; she was on a conference call with NIH Director Collins a week before her death. Kirschstein embodied the spirit of the NIH and was responsible for the career development of innumerable scientists and administrators. ■

Nurik Appointed Director of NIDDK Information Clearinghouses

Jody Nurik has been named director of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Information Clearinghouses. She will oversee long- and short-range plans and operations for the NIDDK's three national health information Clearinghouses and manage the Clearinghouses' support contract. Nurik will also manage the update and production of more than 300 award-winning print and online publications and three national awareness campaigns—bladder control for women, celiac disease, and bowel incontinence.

"Jody is extremely detail-oriented and gifted in big-picture-planning too."

Kathy Kranzfelder
Director, Office of Communications and Public Liaison, NIDDK, NIH

The Clearinghouses disseminate science-based health information to the public, health professionals, and the media. In 2009, the Clearinghouses handled nearly 79,000 information requests, received 6 million visitors to the NIDDK health information website, and distributed more than 1 million publications.

In 2004, Nurik oversaw the transition and establishment of all NIDDK Clearinghouse support contract operations to Circle Solutions, Inc., where she served as project manager. "Jody is extremely detail-oriented and gifted in big-picture-planning too," noted Kathy Kranzfelder, director, Office of Communications and Public Liaison, NIDDK, National Institutes of Health, and former director of the Clearinghouses. "From inquiry response to materials development to inventory database management to exhibit staffing and scheduling to reporting—the Clearinghouses will definitely benefit from new perspective and deep experience from Jody."

Prior to joining the NIDDK, Nurik was director of product marketing at Resolution Health/WellPoint, Inc., where she developed and managed health communications for health care providers and the public. In this role, Nurik led plain language initiatives, outreach campaigns, and market research with physicians and consumers to improve content and design.

Nurik has also managed an information center for the Health Resources and Services Administration, also part of the U.S. Department of Health and Human Services, and has launched adult and pediatric diabetes disease management programs at one of the largest home health companies in the United States. Nurik began her career as a nurse, moving up to supervise urology units of a hospital affiliated with Baylor College of Medicine.

To learn more about the NIDDK Information Clearinghouses, visit *www.niddk.nih.gov.* ■

Crohn's Disease, continued from page 3

Researchers hope the association of RLS with CD may lead to an understanding of fatigue and sleep disturbances associated with CD. Further studies are warranted to evaluate the potential impact that RLS has on the quality of life in patients with CD using the international RLS rating scale.

The National Digestive Diseases Information Clearinghouse, an information dissemination service of the National Institute of Diabetes and Digestive and Kidney Diseases, has fact sheets and easy-to-read booklets about digestive disorders, including CD. For more information and to obtain copies, visit *www.digestive.niddk.nih.gov.* ■

New Fact Sheets

The National Digestive Diseases Information Clearinghouse (NDDIC) has published the following new fact sheets:

- *Colonoscopy* (Spanish)
- *Flexible Sigmoidoscopy* (Spanish)
- H. pylori *and Peptic Ulcers* (Spanish)
- *Liver Biopsy* (Spanish)
- *Lower GI Series* (Spanish)
- *Upper Endoscopy* (Spanish)
- *Upper GI Series* (Spanish)
- *Virtual Colonoscopy* (Spanish)

These publications are available at *www.digestive.niddk.nih.gov.*

Updated Fact Sheets

The NDDIC has updated the following fact sheets:

- *Chronic Hepatitis C: Current Disease Management*
- *Digestive Diseases Statistics for the United States*
- *Gastritis*
- H. pylori *and Peptic Ulcers*
- *Liver Transplantation*
- *Microscopic Colitis: Collagenous Colitis and Lymphocytic Colitis*
- *NSAIDs and Peptic Ulcers*

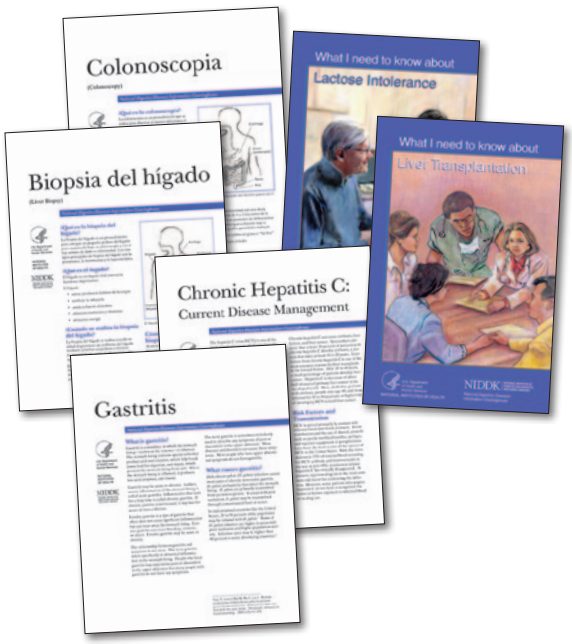
These publications are available at *www.digestive.niddk.nih.gov.*

Updated Easy-to-Read Booklets

The NDDIC has updated the following easy-to-read booklets:

- *What I need to know about Lactose Intolerance*
- *What I need to know about Liver Transplantation*

These publications are available at *www.digestive.niddk.nih.gov.* ■



Upcoming Meetings, Workshops, and Conferences

The National Institute of Diabetes and Digestive and Kidney Diseases Information Clearinghouses will exhibit at the following upcoming event:

Digestive Disease Week

May 7–10 in Chicago.
For more information, visit *www.ddw.org.* ■

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